Title: DIFFERENT EFFECTS OF VASCULAR AGING ON ISCHEMIC PREDISPOSITION IN HEALTHY MEN AND WOMEN

Author(s): Michael O'Rourke, University of New South Wales
Mayooran Namasivayam, St. Vincent's Hospital
Carmel McEniery, University of Cambridge
Ian Wilkinson, University of Cambridge
Yasmin Yasmin, University of Cambridge
John Cockcroft, University of Wales College of Medicine
Barry McDonnell, Cardiff Metropolitan University
Audrey Adji, St Vincent's Clinic, Sydney

DIFFERENT EFFECTS OF VASCULAR AGING ON ISCHEMIC PREDISPOSITION IN HEALTHY MEN AND WOMEN

Short Title: Vascular aging and ischemic predisposition

Authors: Mayooran Namasivayam, Carmel M. McEniery, Ian B. Wilkinson, Yasmin, John R. Cockroft, Barry J. McDonnell, Audrey Adji, Michael F. O'Rourke on behalf of the Anglo-Cardiff Collaborative Trial Investigators

Institutions: Faculty of Medicine, University of New South Wales, Sydney, Australia (M.N., M.F.O.); Division of Experimental Medicine and Immunotherapeutics, University of Cambridge, Cambridge, United Kingdom (C.M.M., I.B.W., Y.); School of Health Sciences, Cardiff Metropolitan University, Cardiff, United Kingdom (J.R.C., B.J.M.); Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia (A.A.).

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Address for Correspondence:

Prof. Michael F. O'Rourke, Suite 810, St. Vincent's Clinic, 438 Victoria Street,

Darlinghurst, New South Wales, Australia, 2010

Phone: +61 2 8382 6874

Fax: + 61 2 8382 6875

Email: m.orourke@unsw.edu.au

Abstract:

Invasive studies of the twentieth century showed the value of aortic pressure-time integrals as markers of myocardial oxygen demand and supply. More recent studies have used these concepts to evaluate mechanisms of ischemic predisposition using non-invasive arterial tonometry in cardiology outpatients. We sought to evaluate the spectrum of myocardial oxygen demand and supply in a large cross-sectional community sample of healthy volunteers, and identify the roles of age, sex and wave reflection. Arterial tonometry was performed in 3682 healthy volunteers. Measures of systolic and diastolic pressure-time integrals and their ratio in addition to cardiac ejection duration were determined and analyzed by age and sex. Multiple regression analyses were performed to identify the mechanisms underlying observations, whilst controlling for confounders (heart rate, height, weight, mean pressure). In a healthy cohort, older women more than men ($p<0.001$) had unfavorable myocardial oxygen supply:demand ratios due to differing effects of vascular aging.

Key words: aging, ischemia, hemodynamics, women, arterial stiffness

Introduction:

Pioneering work by Sarnoff et al.[1] in 1957 showed that when myocardial oxygen demand was measured directly in the isolated, non-failing canine heart, it could be reliably predicted by the area under the aortic pressure curve during the duration of systole. They termed this area the 'tension-time index' (TTI) which can be expressed per beat in mmHg.sec, or more usefully per minute when multiplied by heart rate ($mmHg.sec.min^{-1}$). Extending the work of Sarnoff et al., Buckberg et al.[2] in 1972 evaluated open chested dogs and demonstrated that by additionally measuring the diastolic pressure-time integral, the ratio of endocardial to epicardial blood flow could be evaluated. Using careful control of heart rate and aortic pressures, the authors showed that relative reduction in subendocardial blood flow (i.e. ischemic predisposition) could be reliably predicted from the ratio of the diastolic pressure-time index (DPTI) to TTI, which has been subsequently termed the subendocardial viability ratio (SEVR) or Buckberg Index. Ferro et al.[3] extended this concept to clinical situations by showing a strong linear relationship between stenosis severity and diastolic time at onset of angina in patients with single vessel coronary disease.

Central pressures rather than peripheral blood pressures are required for most accurate determination of myocardial oxygen demand and supply. We have previously evaluated TTI in a cohort of clinical cardiology outpatients and shown that it was increased in older women, and that early wave reflection was a key driver.[4] In this study, we aimed to evaluate how aortic pressure-time analyses, as markers of myocardial oxygen supply and demand, vary across the spectrum of age within a *healthy* cohort, to better understand 'normal' vascular-ventricular interaction changes with aging. Specifically, we aimed to identify the effects of sex in modifying the age-related predisposition to ischemia caused by arterial aging in healthy persons.

Methods:

Data used in this study is not available for public use. This study evaluated 3682 healthy volunteers (1821 males, 1861 females) from the Anglo-Cardiff Collaborative Trial cohort. All subjects gave written informed consent, and all studies were approved by the local research ethics committees. From the original 4001 healthy subjects in this cohort, 319 were excluded for incomplete data [for multivariate analyses] leaving 3682 for final analysis. There were no statistically significant differences between the n = 3682 and n = 4001 cohorts for any hemodynamic parameters. Aortic pressure waveforms were generated from radial arterial tonometric analyses with a Millar SPT-301 high fidelity tonometer (Millar Instruments, Houston, USA) processed with SphygmoCor software (AtCor Medical, Sydney, Australia). Details of subject selection have been published previously.[5] In brief, subjects were excluded if they had hypertension (cuff blood pressure >140 mmHg systolic or 90 mmHg diastolic), diabetes mellitus, serum cholesterol > 6.5 mmol/L, renal disease (defined by clinical history, creatinine > 150 μmmol/L or active urinary sediment), cardiovascular disease defined by clinical history of examination or were on current medication.

Specific variables analysed included TTI, DPTI and SEVR as markers of myocardial oxygen demand, supply capacity and supply:demand ratio, respectively. Additional measures evaluated included cardiac ejection duration (ED), magnitude of forward and reflected pressure waves (measured as P1 height [P1h] and augmented pressure [AP], respectively), and central systolic, diastolic and mean pressures.

Mean age-decade changes in key parameters were initially observed, and subsequent multiple regression analyses determining contributory factors were performed, controlling for confounders of age, height, weight, heart rate and mean arterial pressure. For the variable sex in multiple regressions, men were used as the reference, hence standardized beta, partial eta

and significance values relate to female sex. Statistical procedures were performed using SPSS 25 (IBM Corporation., Armonk, New York).

Results:

Table 1 highlights the significant baseline difference between almost all hemodynamic parameters in men and women. Central hemodynamics were consistently more unfavorable in women. This is despite peripheral blood pressures being higher in men. The higher peripheral blood pressure in men, with concurrently lower central pressures, is consistent with the known greater degree of pulse pressure amplification in men, resulting from their generally taller stature.[6-8]

Table S1 shows the numbers of subjects in each age decade (online supplement). With increasing age, the pattern in change with age in TTI was different by sex (Figure 1). Whilst in men, TTI plateaued after middle age, in women, there was a continued steady increase in TTI as age increased. The trend in DPTI with increasing age decade was similar in men and women, although absolute values for DPTI were greater in men (Figure 2). The fall in DPTI in older age is consistent with the known fall in diastolic blood pressure with advancing age.[9] Combining the trends in TTI and DPTI provides the basis by which SEVR (the supply:demand ratio) becomes more unfavorable in women in older age decades (Figure 3). Figures S1 and S2 show the change in AP and P1h by age decade and gender (online supplement).

Multiple regression models for SEVR and ED are presented in Tables 2 and 3. Table 2 shows that when confounders are adjusted for, both the forward and reflected waves play an important role in the development of an unfavorable myocardial oxygen supply:demand ratio and that there is an interaction between the effects of age and female sex as evidenced by a significant age*female sex interaction. Both the forward and reflected wave are important

contributors to SEVR despite confounder correction. Once ejection duration is factored into the multiple regression, however, the interaction effect of the age*female sex interaction becomes non-significant and the contribution of wave reflection becomes less important. When the determinants of ejection duration are evaluated with multiple regression, wave reflection is associated with a considerably higher standardized beta and partial Eta squared at a considerably higher level of statistical significance than forward wave magnitude (Table 3). Standardized beta values in Tables 2 and 3, highlight the positive and negative associations of different hemodynamic variables with SEVR. It is worth noting the positive associations of AP, P1h, mean arterial pressure and the negative associations of age, female sex, ejection duration and heart rate (see Discussion). Tables S2-S4 show multiple regression relationships for SEVR in the cohort with subjects grouped into those aged <30 years, aged 30-60 years and >60 years (online supplement). These show that the role of wave reflection in determining SEVR is most pronounced in older persons. Table S5 shows cohort multiple regression relationships for TTI (online supplement).

Discussion:

Vascular Aging and Ischemic Predisposition

Sarnoff et al.[1] showed a strong correlation of TTI to myocardial oxygen demand in invasive studies of isolated non-failing canine hearts. They showed that aortic pressure, rather than cardiac output or external heart work, was the primary driving factor for myocardial oxygen demand. Indeed, the authors demonstrated that the contribution of flow (cardiac output) to myocardial oxygen demand was mediated by its effect on mean systolic pressure.

Extending this work, Buckberg et al.[2] showed that subendocardial ischemia could be induced despite normal or supranormal coronary blood flow, since DPTI was dependent on the duration and driving coronary pressure during diastole. The authors showed that

subendocardial ischemia could be predicted by relating myocardial oxygen demand, expressed as TTI, to DPTI as the DPTI:TTI ratio, also termed the subendocardial viability ratio (SEVR), later named the "Buckberg Index".

Through analysis of aortic pressure alone, these investigators developed a means of predicting predisposition to ischemia in the absence of coronary stenosis.[10] Using a large cohort of community sampled healthy volunteers, we sought to evaluate the trends in these parameters of aortic pressure-time, namely TTI, DPTI and SEVR, across a spectrum of age and sex.

Through age-decade analysis, we have shown that especially in women, there is a steady increase in TTI with age, which when combined with the natural fall in DPTI in older persons, portends an unfavorable SEVR in older females. Using multiple regression analyses, we have shown that in addition to the contribution of age and sex to ischemic predisposition, there is an interaction between age and sex, such that the influences of sex can modify age effects. Furthermore, we have shown that whilst the forward and reflected waves are important in determining SEVR, even when confounders are adjusted for, the primary contribution of wave reflection is driven by its relationship with cardiac ejection duration.

Whilst we would argue that this suggests that increased wave reflection prolongs cardiac ejection duration and augments systolic load, an alternative explanation might be that varying ejection duration could alter the timing of wave reflection. Our view, however, not only holds with traditional views on the determinants of ejection duration,[11,12] but is also supported by the detailed mechanistic work done by Buckberg et al.[2], who showed that increasing aortic pressure (using supravalvular constriction) prolonged cardiac ejection duration and subsequently contributed to subendocardial ischemia.

The negative effects of female sex, aging, ejection duration and wave reflection (each associated with adverse vascular-ventricular interaction in the literature[4-9]) on SEVR are seen by the negative standardized beta values in Table 2. The negative standardized beta for heart rate as a predictor of SEVR in multiple regression analyses in Table 2 confirms the increasing propensity to ischemia with increasing heart rate, caused by reduced diastolic perfusion time.[1,3] This suggests our findings would be more pronounced in the setting of physical exertion and elevated heart rate, which is relevant in the clinical consideration of exertional ischemia. Increased mean arterial pressure was associated with a better SEVR in our cohort (positive standardized beta), however it should be noted that our cohort was a healthy, normotensive one in both genders. Once arterial pressures rise into the pathological range, elevated mean pressures could translate to elevated systolic load which may not be counterbalanced by the benefits of increased coronary perfusion pressure.

Our findings highlight how vascular aging can modify the aortic pressure-time relationships known to represent myocardial oxygenation supply and demand. These aging processes are different in men and women and could lead to the predisposition to subendocardial ischemia quite distinctly to the processes of atherosclerosis and coronary stenosis which dominate current discussions on ischemic heart disease. Our findings have potential implications for future assessment and management of ischemic heart disease, particularly in the setting of chest pain with normal coronary arteries, which is particularly problematic in women, whereby this condition is known to lead to adverse cardiovascular outcomes with no clear pathophysiological explanation.[13] The very high female to male gender ratio (10:1) in acute Takotsubo syndrome, an extreme example of myocardial ischemia in the absence of coronary stenosis, may be a condition where our findings may be relevant.[14-16]

In addition to adverse clinical outcomes, chest pain with normal angiography can also lead to adverse psychological outcomes.[17] Thinking on ischemia should not be limited to the

coronary artery lumen and must re-evaluate the balance of myocardial energy supply and demand that was at the forefront of consideration by pioneering physiologists, before coronary artery pathology was so accessible to cardiologists both conceptually and literally. Whilst microvascular dysfunction[18,19]is considered in the discussion on predisposition to ischemia in the absence of coronary disease, we propose that our findings suggest that macrovascular (aortic) dysfunction must also be considered. Even in patients with coronary artery disease, large artery stiffness has been shown to predict ischemic threshold.[20] A potential mechanism is suggested by the findings of this study.

The underlying basis for more adverse age-related change in ventriculo-arterial interaction in women is not known. Previous work has also shown that pulsatile hemodynamics and ventriculo-arterial interaction in women is more unfavorable.[8,21-23] Postulated explanations include hormonal differences[24,25]and differing body size.[6-8] We observed effects irrespective of height and weight (and hence body mass index), therefore differing body shape may be of importance. Future work must further investigate these and other mechanisms.

Our findings support our earlier observations of hemodynamic factors related to myocardial oxygen demand in a community cohort of cardiology patients.[4] This time, in a cohort of healthy volunteers, once again, age, female sex, wave reflection and cardiac ejection duration were important mediators of myocardial oxygenation as assessed using aortic pressure-time analysis. Such factors are therefore likely part of 'normal' vascular aging in healthy individuals, whereby there is a transition toward ischemic predisposition in older women particularly. Such changes may well contribute to the extreme sex and age difference in Takotsubo syndrome.[14-16] The detrimental vascular aging phenomenon in women could occur much in the same way that we see progression of bone density loss and muscle mass loss in otherwise healthy older women.

Limitations

Despite observations using detailed tonometric assessment and validated transfer function in over 3,500 healthy volunteers, our non-invasive approach carries limitations which must be considered when interpreting our data. We measured (approximated) aortic pressure alone and did not measure left ventricular pressure. This has two effects. Firstly, for DPTI, the definition used by Buckberg et al.[2] was the pressure difference between the aorta and left ventricle during diastole. As we cannot measure the left ventricular pressure, we assume that this is zero during diastole, which we feel is not unreasonable in a healthy cohort. As left ventricular diastolic pressures naturally rise with age, our estimates of DPTI in older persons are probably overestimates (as elevated left ventricular diastolic pressure reduces coronary perfusion pressure), which actually means that our findings might have been more marked in this age group, as myocardial oxygen supply capacity might have been less than we approximated.[10] Secondly, the lack of left ventricular pressure measurement means that we could not account for isovolumetric contraction and relaxation. Increase in left ventricular pressure leads increase in aortic pressure and fall in left ventricular pressure lags fall in aortic pressure. This lack of accounting for the isovolumetric components of the cardiac cycle is estimated to overestimate DPTI by 10-15% and underestimate TTI by 10-15%.[10] Once again, this means that our myocardial oxygen supply capacity is overestimated and furthermore, myocardial oxygen demand is underestimated, meaning that our findings would have been more marked still, when the true SEVR is considered in older persons. It should be noted that Buckberg et al.[2] themselves did not directly measure left ventricular pressure, but rather measured left atrial pressure as a marker of left ventricular diastolic pressure.

Another limitation is inherent in the terminology tension time index (TTI) which ascribes tension as one of the determinants of myocardial oxygen demand. This is an unfortunate use of terminology adopted initially by Sarnoff et al.[1] and continued since in the literature, as

tension is not measured in their description and derivation of TTI. Indeed, tension is important to myocardial oxygenation, but cannot be determined in the TTI as described, without knowing ventricular geometry. True tension is dependent on the Law of LaPlace and relates to ventricular dimensions and wall thickness.[26] We did not have these measurements, and as such, any differences in ventricular geometry across our cohort were unaccounted for. This is relevant when the sex differences reported are considered because men will generally have larger ventricular dimensions to women, and as such, our estimate of TTI will be underestimated in men as compared to women. We do note, however, that although in the original description of TTI, Sarnoff et al.[1] did not measure ventricular dimensions or wall thickness, the authors nonetheless showed good invasive correlation of aortic pressure-time parameters to directly measured myocardial oxygen demand. Furthermore, although our study cohort were selected to be healthy, the burden of coronary artery disease was not known. Whilst invasive coronary assessment is impractical and unethical in a healthy cohort of this size, the availability of computed tomography coronary assessment means that future studies could incorporate coronary disease burden into analyses.

Future studies which could build on the work here might also use magnetic resonance imaging or contrast/strain echocardiography to not only incorporate left ventricular dimensions and left ventricular mass but also directly assess for subendocardial ischemia, particularly with stress, to evaluate whether those with more unfavorable SEVR profiles are indeed predisposed to observable subendocardial ischemia with stress. In addition to coronary atheroma burden, microvascular dysfunction[18,19] would be useful to measure in such future studies.

Perspectives:

Myocardial oxygenation has been directly invasively correlated to aortic pressure-time analyses by pioneering physiologists of the 20th century. Adapting these methods to non-invasive measures of aortic pressure-time parameters, we have demonstrated that with aging, there is an unfavorable trend in the myocardial oxygen supply:demand ratio in older women particularly. Both the forward and reflected pressure wave are important contributors to this process and the role of wave reflection is particularly driven by its effect on cardiac ejection duration. Ischemic heart disease is more complex than coronary lumen stenosis. Vascular aging in the large arteries alters central hemodynamics and can predispose to myocardial ischemia irrespective of coronary artery status, particularly in women.

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Disclosures:

Dr Michael F. O'Rourke is a founding director of AtCor Medical and AortaMate Pty. Ltd., Sydney, companies which manufacture arterial pulse wave analysis technology. The other authors report no disclosures.

References:

1. Sarnoff SJ, Braunwald E, Welch GH Jr., Case RB, Stainsby WN, Macruz R. Hemodynamic determinants of oxygen consumption of the heart with special reference to tension-time index. *Am J Physiol*. 1958;192:148-156.
2. Buckberg GD, Fixler DE, Archie JP, Hoffman JIE. Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circ Res*.1972;30:67-81.
3. Ferro G, Duilio C, Spinelli L, Liucci GA, Mazza F, Indolfi C. Relation between diastolic perfusion time and coronary artery stenosis during stress-induced myocardial ischemia. *Circulation*. 1995;92:342-347.
4. Namasivayam M, Adji A, O'Rourke MF. Influence of aortic pressure wave components determined noninvasively on myocardial oxygen demand in men and women. *Hypertension*. 2011;57:193-200.
5. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity – the Anglo Cardiff Collaborative Trial. *J Am Coll Cardiol.* 2005;46:1753-1760.
6. Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME, London GM. Influence of body height on pulsatile arterial hemodynamic data. *J Am Coll Cardiol*. 1998;31:1103-1109.
7. Smulyan H, Asmar RG, Rudnicki A, London GM, Safar ME. Comparative effects of aging in men and women on properties of the arterial tree. *J Am Coll Cardiol*. 2001;37:1374-1380.
8. Hayward CS, Kelly RP. Gender related differences in the central arterial pressure waveform. *J Am Coll Cardiol*. 1997;1863-1871.

9. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation*. 1997;96: 308-315.
10. Hoffman JIE, Buckberg GD. The myocardial supply:demand ratio – a critical review. *Am J Cardiol*. 1978;41:327-332.
11. Wiggers CJ. Studies on the consecutive phases of the cardiac cycle: II. The laws governing the relative durations of ventricular systole and diastole. *Am J Physiol*. 1921;56:415-438.
12. Braunwald E, Sarnoff SJ, Stainsby WN. Determinants of duration and mean rate of ventricular ejection. *Circ Res*. 1958;6:319:325.
13. Johnson BD, Shaw LJ, Pepine CJ, Reis SE, Kelsey SF, Sopko G, Rogers WJ, Mankad S, Sharaf BL, Bittner V, Bairey Merz CN. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI sponsored Women's Ischemia Syndrome Evaluation (WISE) study. *Eur Heart J*. 2006;27:1408-1415.
14. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International expert consensus document on Takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J*. 2018;39:2032-2046.
15. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM,

Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International expert consensus document on Takotsubo syndrome (part II): diagnostic workup, outcome, and management. *Eur Heart J*. 2018;39:2047-2062.

16. Ghadri JR, Kato K, Cammann VL, Gili S, Jurisic S, Di Vece D, Candreva A, Ding KJ, Micek J, Szawan KA, Bacchi B, Bianchi R, Levinson RA, Wischnewsky M, Seifert B, Schlossbauer SA, Citro R, Bossone E, Münzel T, Knorr M, Heiner S, D'Ascenzo F, Franke J, Sarcon A, Napp LC, Jaguszewski M, Noutsias M, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschöpe C, Pieske BM, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Hasenfuß G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Empen K, Felix SB, Delmas C, Lairez O, El-Battrawy I, Akin I, Borggrefe M, Horowitz J, Kozel M, Tousek P, Widimský P, Gilyarova E, Shilova A, Gilyarov M, Winchester DE, Ukena C, Bax JJ, Prasad A, Böhm M, Lüscher TF, Ruschitzka F, Templin C. Long-term prognosis of patients with Takotsubo syndrome. *J Am Coll Cardiol*. 2018;72:874-882.
17. Hanssen TA, Iqbal A, Forsdahl SH, Trovik T, Schirmer H. Changes in symptoms of anxiety and depression following diagnostic angiography: a prospective cohort study. *Eur Heart J: Qual Care Clin Outcomes*. 2018;4:106-112.
18. Campisi R, Marengo F. Coronary microvascular dysfunction in women with nonobstructive ischemic heart disease as assessed by positron emission tomography. *Cardiovasc Diagn Ther*. 2017;7:196-205.

19. Liu A, Wijesundra RS, Liu JM, Forfar JC, Channon KM, Jerosch-Herold M, Piechnik SK, Neubauer S, Kharbanda RK, Ferreira VM. Diagnosis of microvascular angina using cardiac magnetic resonance. *J Am Coll Cardiol*. 2018;71:969-979.
20. Kingwell BA, Waddell TK, Medley TL, Cameron JD, Dart AM. Large artery stiffness predicts ischemic threshold in patients with coronary artery disease. *J Am Coll Cardiol*. 2002;40:773-779.
21. Coutinho T, Pellikka PA, Bailey KR, Turner ST, Kullo IJ. Sex differences in the associations of hemodynamic load with left ventricular hypertrophy and concentric remodeling. *Am J Hypertens*. 2016;29:73-80.
22. Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. *J Am Coll Cardiol*. 2013;61:96-103.
23. London GM, Guerin AP, Pannier B, Marchais SJ, Stimpel M. Influence of sex on arterial hemodynamics and blood pressure. *Hypertension*. 1995;26:514-519.
24. Takahashi K, Miura S, Mori-Abe A, Kawagoe J, Takata K, Ohmichi M, Kurachi H. Impact of menopause on the augmentation of arterial stiffness with aging. *Gynecol Obstet Investig*. 2005;60:162-166.
25. Zaydun G, Tomimaya H, Hashimoto H, Arai T, Koji Y, Yambe M, Motobe K, Hori S, Yamashina A. Menopause is an independent factor augmenting the age-related increase in arterial stiffness in the early post-menopausal phase. *Atherosclerosis*. 2006;184:137-142.
26. McDonald RH, Taylor RR, Cingolani HE. Measurement of myocardial developed tension and its relation to oxygen consumption. *Am J Physiol*. 1966;211:667-673.

Novelty and Significance

What is New?

- Using concepts developed from invasive physiology relating aortic pressure-time analyses to myocardial oxygenation, we studied the distribution of myocardial oxygen supply and demand in a large cohort of healthy volunteers.
- Even in healthy individuals, increasing age and female sex led to unfavorable myocardial oxygen supply:demand ratio.
- Both forward and reflected waves were important, with wave reflection exerting its effect primarily through its influence on cardiac ejection duration.

What is Relevant?

- Vascular aging predisposes to myocardial ischemia, even in healthy individuals, and particularly in women.
- Such considerations are potentially important for future assessment and management of myocardial ischemia.

Summary

- Vascular aging influences the predisposition to ischemia, irrespective of coronary artery status, even in healthy individuals.
- Discussion on ischemic heart disease should incorporate the complexities that extend beyond coronary lumen stenosis, particularly in older women.

List of Figures:

Tables:

Table 1: Subject characteristics by sex.

Variable	Males (n = 1821)	Females (n = 1861)	Significance
Age (yrs)	51.2 (18.0)	53.2 (16.4)	0.0004
Height (m)	1.74 (0.09)	1.63 (0.08)	<0.0001
Weight (kg)	78.9 (14.0)	69.2 (13.5)	<0.0001
BMI (kg/m^2)	26.2 (4.0)	26.0 (4.6)	NS (0.1596)
HR (bpm)	65.0 (10.9)	68.3 (10.3)	<0.0001
MAP (mmHg)	93.2 (7.5)	91.2 (8.4)	<0.0001
ED (ms)	313.0 (28.2)	320.5 (27.8)	<0.0001
TR (ms)	144.4 (16.5)	134.0 (14.9)	<0.0001
AP (mmHg)	7.9 (6.2)	11.7 (6.6)	<0.0001
P1h (mmHg)	27.4 (4.8)	25.8 (5.6)	<0.0001
TTI ($mmHg.sec.min^{-1}$)	2088.9 (295.1)	2215.0 (320.1)	<0.0001
DPTI ($mmHg.sec.min^{-1}$)	3503.7 (345.3)	3257.4 (349.5)	<0.0001
SEVR (%)	171.2 (30.3)	149.9 (25.5)	<0.0001
pSBP (mmHg)	125.3 (9.2)	121.5 (11.4)	<0.0001
pDBP (mmHg)	77.2 (6.8)	74.5 (7.3)	<0.0001
pPP (mmHg)	48.1 (8.1)	47.0 (9.8)	0.0002
cSBP (mmHg)	113.6 (10.1)	112.9 (12.1)	NS (0.0570)
cDBP (mmHg)	78.1 (6.9)	75.4 (7.5)	<0.0001
cPP (mmHg)	35.5 (7.9)	37.5 (10.0)	<0.0001
PP Amp	1.38 (0.21)	1.28 (0.19)	<0.0001

All values presented are mean(SD).

Abbreviations: AP: augmented pressure; BMI: body mass index; cDBP: central diastolic blood pressure; cPP: central pulse pressure; cSBP central systolic blood pressure; DPTI: diastolic pressure time index; ED: ejection duration; HR: heart rate; MAP: mean arterial pressure; pDBP: peripheral diastolic blood pressure; PP Amp: pulse pressure amplification ratio; pPP: peripheral pulse pressure; pSBP: peripheral systolic blood pressure; P1h: P1 height; SEVR: sub-endocardial viability ratio; TR: reflection time; TTI: tension time index.

Table 2: Multiple regression model for subendocardial viability ratio, without and then with ejection duration as a covariate.

Variable	F	Partial Eta Sq.	Sig.	Std. beta†	Sig. (beta)
SEVR					
Age	63.4	0.017	<0.001	-0.104	<0.001
Female sex	56.0	0.015	<0.001	-0.145	<0.001
Height	11.5	0.003	0.001	0.045	<0.001
Weight	42.0	0.011	<0.001	-0.072	<0.001
Heart rate	6303.1	0.632	<0.001	-0.846	<0.001
Mean arterial pressure	145.2	0.038	<0.001	0.124	<0.001
AP	393.1	0.097	<0.001	-0.303	<0.001
P1h	379.5	0.094	<0.001	-0.179	<0.001
Age*female sex	8.7	0.002	0.003	-	-

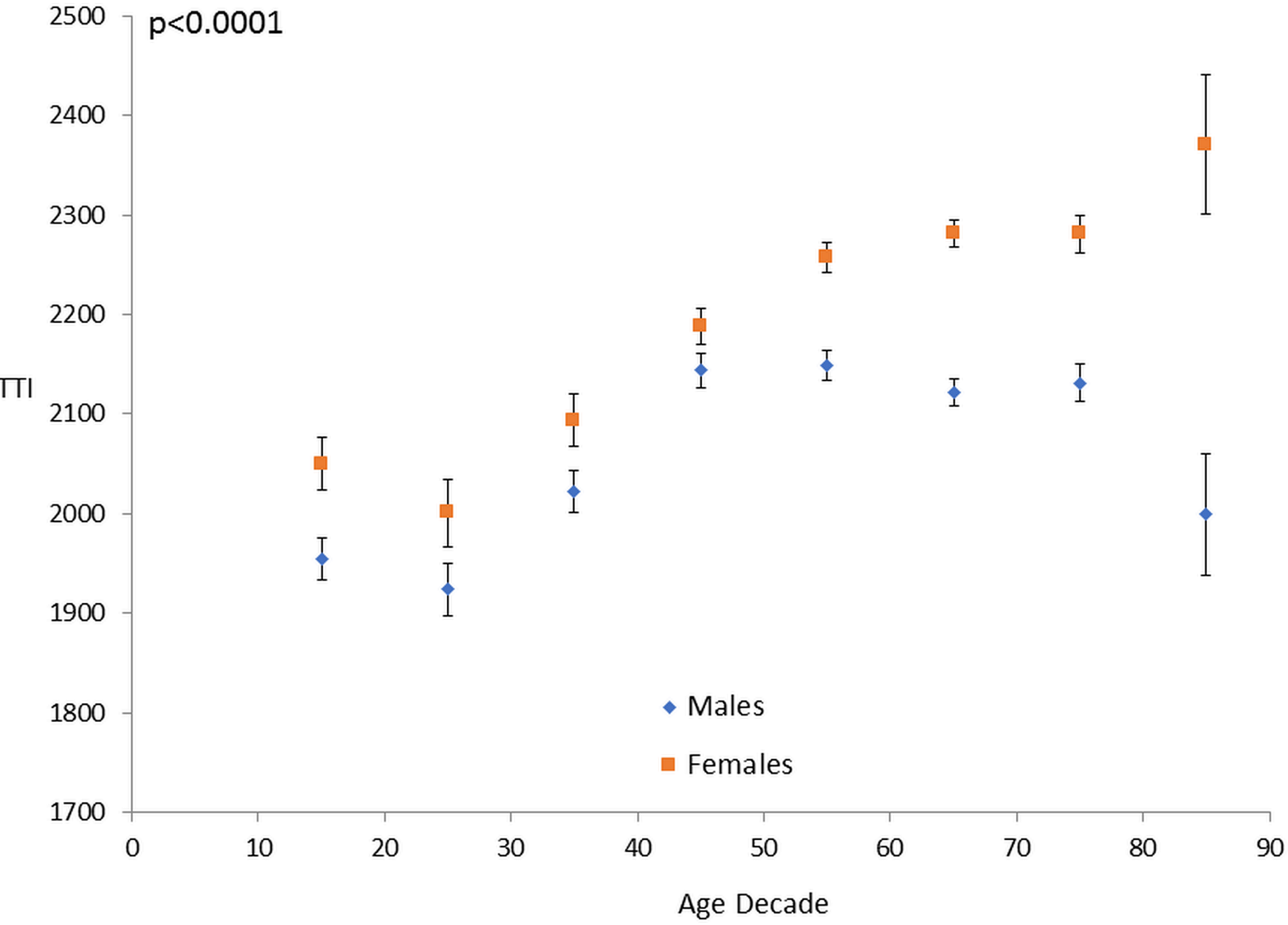
Variable	F	Partial Eta Sq.	Sig.	Std. beta†	Sig. (beta)
SEVR					
Age	75.5	0.020	<0.001	-0.053	<0.001
Female sex	7.9	0.002	0.005	-0.031	<0.001
Height	2.9	0.001	NS	0.010	NS
Weight	1.1	0.000	NS	-0.006	NS
Heart rate	39292.8	0.915	<0.001	-1.293	<0.001
Mean arterial pressure	503.1	0.121	<0.001	0.111	<0.001
AP	232.3	0.060	<0.001	-0.115	<0.001
P1h	1564.7	0.299	<0.001	-0.179	<0.001
Age*female sex	0.5	0.000	NS	-	-
ED	12228.0	0.769	<0.001	-0.749	<0.001

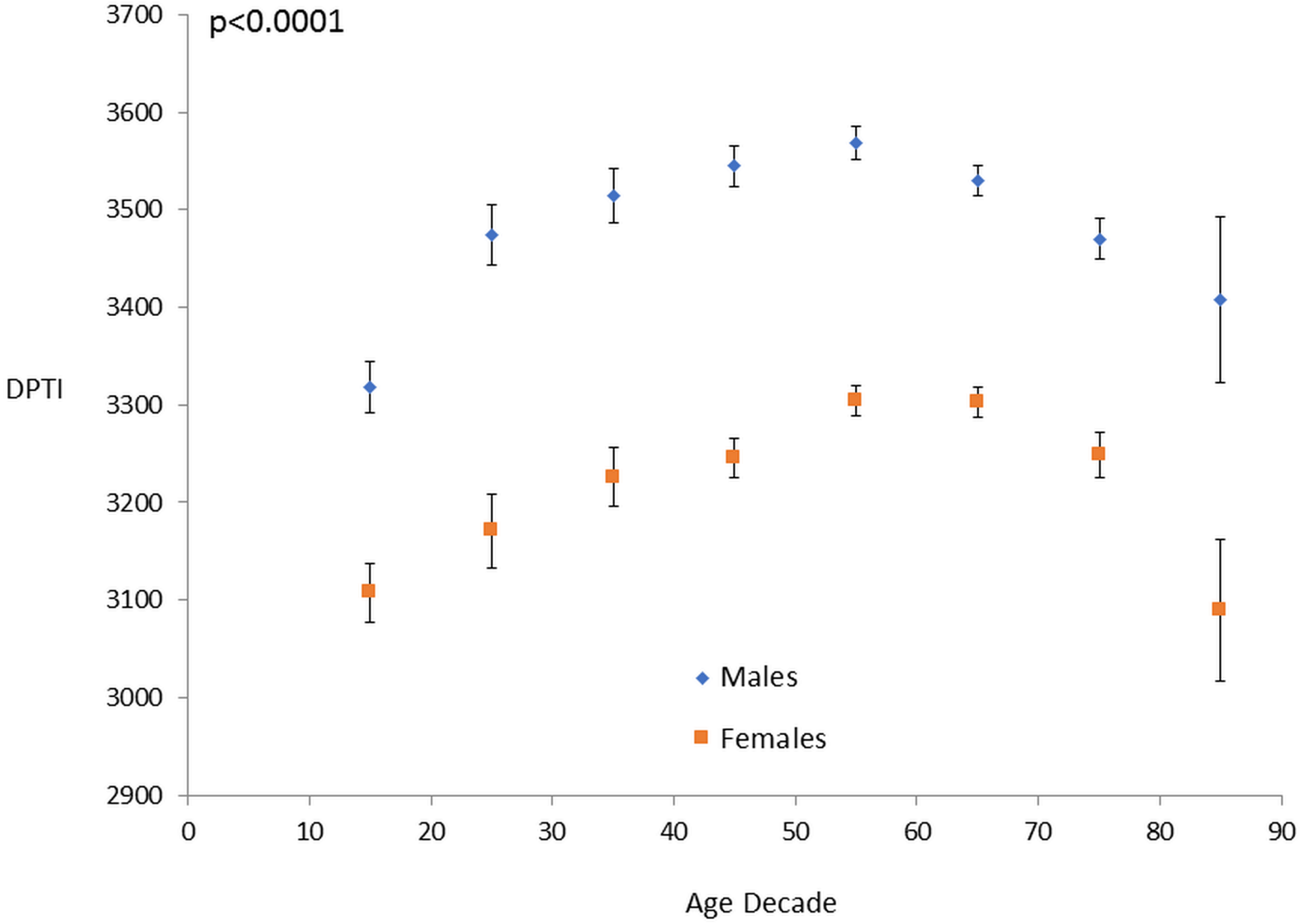
Abbreviations: AP: augmented pressure (mmHg), ED: ejection duration (ms), P1h (P1 Height) (mmHg), SEVR: subendocardial viability ratio (%). † Age*female sex term not included in model for determination of standardized beta.

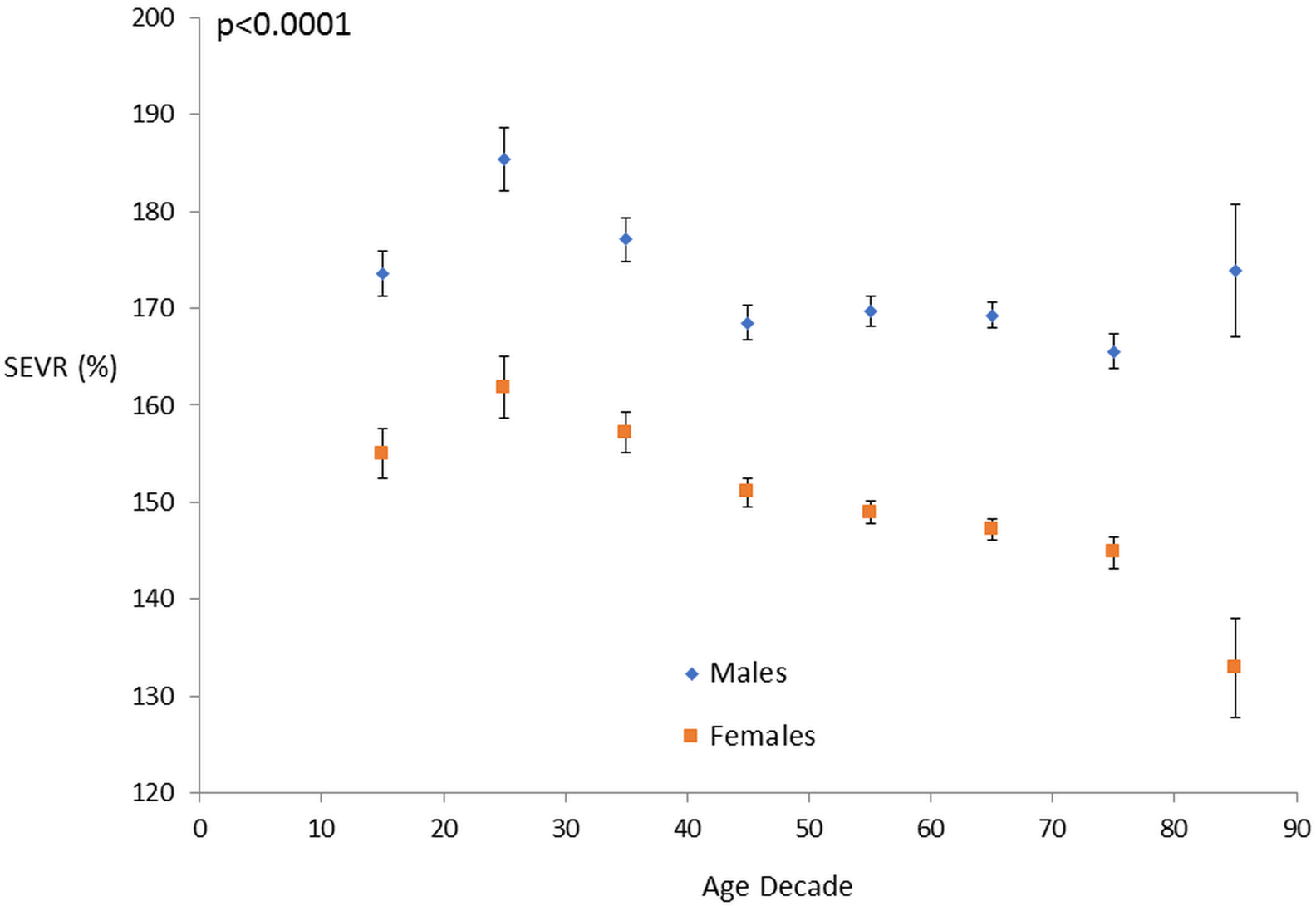
Table 3: Multiple regression model for ejection duration.

Variable	F	Partial Eta Sq.	Sig.	Std. beta†	Sig. (beta)
ED					
Age	18.5	0.005	0.005	0.068	<0.001
Female sex	48.7	0.013	<0.001	0.151	<0.001
Height	8.6	0.002	0.003	-0.046	0.002
Weight	46.2	0.012	<0.001	0.089	<0.001
Heart rate	2263.4	0.381	<0.001	-0.596	<0.001
Mean arterial pressure	2.1	0.001	NS	-0.017	NS
AP	197.0	0.051	<0.001	0.250	<0.001
P1h	0.3	0.000	NS	0.000	NS
Age*female sex	8.8	0.002	0.003	-	-

Abbreviations: AP: augmented pressure (mmHg), ED: ejection duration (ms), P1h (P1 Height) (mmHg). † Age*female sex term not included in model for determination of standardized beta.


p<0.0001
2500
2400
2300
2200
2100
2000
1900
1800
1700
TTI
0
10
20
30
40
50
60
70
80
90
Age Decade
Males
Females


p<0.0001
DPTI
3700
3600
3500
3400
3300
3200
3100
3000
2900
0
10
20
30
40
50
60
70
80
90
Age Decade
Males
Females


p<0.0001
SEVR (%)
200
190
180
170
160
150
140
130
120
0
10
20
30
40
50
60
70
80
90
Age Decade
Males
Females